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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,026	10/20/2001	William D. Picking	UOK 5320.1	9340
321	7590	11/07/2006	EXAMINER	
SENNIGER POWERS ONE METROPOLITAN SQUARE 16TH FLOOR ST LOUIS, MO 63102			DEVI, SARVAMANGALA J N	
			ART UNIT	PAPER NUMBER
			1645	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/830,026

Applicant(s)

PICKING ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 13-18, 21, 22, 25 and 101-122 ~~is/are~~ pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 13-18, 21, 22, 25 and 101-122 ~~is/are~~ rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 52104 & 81006
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☒ Other: Requested p. 1 of 82701 IDS

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 05/21/04 in response to the non-final Office Action mailed 11/21/03. With this, Applicants have amended the specification and the claims.

Election

2) Acknowledgment is made of Applicants' election filed 08/10/06, with traverse, of invention II, in response to the written lack of unity mailed 07/10/06. Applicants' traversal is on the grounds that the claims are directed to methods for the production of a purified IpaC or SipC protein, which methods vary only in the polynucleotide sequence used. Applicants contend that the general inventive concept linking inventions I and II lies not in the structure of SEQ ID NO: 1 (SipC) or SEQ ID NO: 2 (IpaC), but rather in the claimed generic methods. Applicants state that SEQ ID NO: 1 is the native amino acid sequence of the SipC protein of *Salmonella typhimurium*, and SEQ ID NO: 2 is the native amino acid sequence of the IpaC protein of *Shigella flexneri*. Applicants point to Table 1 on pages 3-5 of the specification and assert that there are significant structural and functional similarities between the two sequences. Applicants opine that any search of the prior art and examination involving invention I therefore will substantially co-extend with the search and examination of invention II. Applicants further cite MPEP § 803.04 and state that normally ten sequences constitute a reasonable number for examination purposes and that in most cases up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction. With this, Applicants conclude that the examination of two amino acid sequences that have structural and functional similarity does not impose a serious burden on the Office.

Applicants' arguments have been carefully considered, but are not persuasive. First, contrary to Applicants' assertion, the SipC and IpaC sequences of SEQ ID NO: 1 and SEQ ID NO: 2 respectively do not represent polynucleotide sequences, but polypeptide sequences. As set forth under art rejections below, the claimed generic methods were known in the art at the time of the invention. Therefore, the claimed generic methods do not define over the prior art. The inventive concept linking the inventions, i.e., the claimed generic method, therefore is not a unifying feature. The two invasin proteins having the structure or amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 2 represent two proteins which do not share significant structure such that a sequence search for one would yield all relevant prior art on the other. The two invasin proteins require separate,

individual, and non-coextensive structure searches and burdensome review or analysis of sequence search reports. A search for *Salmonella typhimurium* and a search for *Shigella flexneri* would not be co-extensive. Furthermore, all the generic claims that do not recite SEQ ID NO: 1 or SEQ ID NO: 2 would require a broader search beyond SEQ ID NO: 1, SEQ ID NO: 2, and beyond *Salmonella typhimurium*, and *Shigella flexneri*. Applicants' argument that normally up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction is misplaced, for two reasons: (a) This part of the MPEP concerns EST cases involving nucleotide sequences; and (b) The instant application is a non-EST application and involves structurally non-identical amino acid sequences.

However, upon further consideration, the lack of unity set forth previously has been hereby modified. The two recited amino acid sequences are now considered as two invasin protein species. The invasin protein having the amino acid sequence of SEQ ID NO: 2 (IpaC) is considered as the elected species and the claims reciting this species have been examined. The invasin protein having the amino acid sequence of SEQ ID NO: 1 is considered as the non-elected species and is currently withdrawn from further consideration. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Status of Claims

3) Claims 1-7, 10, 12, 19, 20, 23, 24, 26, 29-33, 38-44, 47, 51-56, 70, 72, 73, 77-80, 82-87, 90-92, 94-96 and 98-100 have been canceled via the amendment filed 05/21/04.

Claims 13, 14, 21, 22, 25 and 103 have been amended via the amendment filed 05/21/04.

New claims 104-122 have been added via the amendment filed 05/21/04.

Claims 13-18, 21, 22, 25 and 101-122 are pending.

Claims 13-18, 21, 22, 25 and 101-122 are under examination.

Information Disclosure Statements

4) Acknowledgment is made of Applicants' information disclosure statements filed 05/21/04 and 08/10/06. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Sequence Listing

5) Acknowledgment is made of Applicants' raw sequence listing and CRF which have been

entered on 07/06/04.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 9 of the Office Action mailed 11/21/03 due to sequence non-compliance is withdrawn in light of Applicants' amendment to the specification.

7) The objection to the specification made in paragraph 10 of the Office Action mailed 11/21/03 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

8) The rejection of claim 13 made in paragraph 11(a) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

9) The rejection of claim 14 made in paragraph 11(b) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claims 14 and 25 made in paragraph 11(c) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

11) The rejection of claims 13 and 14 made in paragraph 11(d) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.

12) The rejection of claims 13, 14 and 25 made in paragraph 11(e) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

13) The rejection of claims 13, 14 and 25 made in paragraph 11(f) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

14) The rejection of claims 13, 14 and 25 made in paragraph 11(g) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

- 15)** The rejection of claims 13, 14 and 25 made in paragraph 11(h) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 16)** The rejection of claims 13, 14 and 25 made in paragraph 11(i) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 17)** The rejection of claims 13, 14 and 25 made in paragraph 11(j) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 18)** The rejection of claims 13, 14 and 25 made in paragraph 11(k) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 19)** The rejection of claims 13, 14 and 25 made in paragraph 11(l) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 20)** The rejection of claims 22 and 103 made in paragraph 11(m) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.
- 21)** The rejection of claims 13, 14 and 25 made in paragraph 11(n) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn upon further consideration.
- 22)** The rejection of claims 16 and 17 made in paragraph 11(o) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.
- 23)** The rejection of claims 101 and 102 made in paragraph 11(p) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.
- 24)** The rejection of claim 21 made in paragraph 11(q) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

- 25)** The rejection of claim 14 made in paragraph 11(r) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.
- 26)** The rejection of claim 21 made in paragraph 11(r) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn.
- 27)** The rejection of claims 101-103 made in paragraph 11(s) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.
- 28)** The rejection of claims 15-18, 21 and 22 made in paragraph 11(s) of the Office Action mailed 11/21/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.
- 29)** The rejection of claims 13-16, 21, 22, 101 and 103 made in paragraph 14 of the Office Action mailed 11/21/03 under 35 U.S.C. § 102(b) as being anticipated by Picking *et al.* (*Protein Expression and Purification* 8: 401-408, 1996 - Applicants' IDS), is withdrawn.
- 30)** The rejection of claims 13, 14, 16, 22, 101 and 103 made in paragraph 15 of the Office Action mailed 11/21/03 under 35 U.S.C. § 102(b) as being anticipated by Leong *et al.* (*EMBO J.* 9: 1979-1989, 1990), is withdrawn.
- 31)** The rejection of claims 25 made in paragraph 17 of the Office Action mailed 11/21/03 under 35 U.S.C. § 103(a) as being unpatentable over Oaks *et al.* (*Clin. Diagnost. Lab. Immunol.* 3: 242-245, 1996) in view of Comb *et al.* (US 5,834,247) and/or Anilionis *et al.* (US 5,196,338), Thorne (US 5,552,294) and Seed (US 5,726,293), is withdrawn.

Rejection(s) Maintained

- 32)** The rejection of claims 13-18, 21, 22 and 101-103 made in paragraph 13 of the Office Action mailed 11/21/03 under 35 U.S.C. § 102(b) as being anticipated by Paul *et al.* (*Human Gene Therapy* 8: 1253-1262, 01 July 1997, already of record), is maintained for reasons set forth therein and herebelow.

New claims 105 and 112 are now added to this rejection.

Applicants cite MPEP 2131 and contend that a claim is anticipated under 35 U.S.C. § 102

only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Applicants' provide a description of Paul's method from column 2 of Paul's page 1255 and contend that Paul *et al.* do not describe each and every element of claims 13 and 14, because claims 13 and 14 both require removing the protein denaturant from the purified invasive protein until the concentration of the protein denaturant is at the minimum concentration necessary to maintain the solubility of the purified invasin protein (step f) and rapidly diluting the purified invasin protein into a volume of denaturant-free solution (step g). Applicants acknowledge that Paul *et al.* make a statement regarding empirically determining optimal dilutions to avoid aggregation during refolding, but argue that there is no mention in Paul *et al.* of removing denaturant to a minimum concentration necessary to maintain solubility of the purified invasin protein, followed by rapid dilution of the purified invasin protein into a volume of denaturant-free solution. Applicants state that, in contrast, Paul *et al.* describe refolding the proteins by slowly and sequentially dialyzing away the denaturant. Applicants disagree with the Office's assertion that 'rapid' dilution into a denaturant-free solution is inherent in Paul *et al.* Applicants argue that in relying on inherency, the Office must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent feature necessarily flows from the teachings of the applied prior art. Applicants assert that the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient for inherency. Applicants allege that no such showing has been made by the Office as to rapid dilution of purified invasin protein into a volume of denaturant-free solution and that the only evidence supplied by the Office in support of inherency is a statement that the final recombinant invasin product remained soluble and biologically functional. Applicants state that the protein renaturation process described by Paul *et al.* involves dialyzing the protein-containing samples against buffer 1 (which contained 6M urea) and then sequential diluting the dialysis buffer two-fold in buffer 1 (without urea) eight times at 'intervals of at least 2 hours' and dialyzing the samples against buffer 2 without urea or guanidine-HCl. Applicants submit that Paul *et al.* do not perform a rapid dilution into a denaturant-free solution, but rather perform a sequential dilution over the course of at least 16 hours, and step g of claims 13 and 14 (i.e., rapidly diluting the purified invasion protein into a volume of denaturant-free solution) can not be said to be inherent in Paul *et al.* Applicants further provide the footnote stating

that: (a) Invasins described in Paul *et al.* are from *Yersinia pseudotuberculosis* and are thus different from the invasin proteins described in the present application; (b) It cannot therefore be assumed that the invasins of Paul *et al.* would have the same characteristics as the invasins of the present invention; and (c) The purification strategy for the invasins of Paul *et al.* would thus not necessarily be the same as for the invasin proteins of the present invention.

Applicants' arguments have been carefully considered, but are not persuasive. First, contrary to Applicants' assertion, the 'invasin protein' recited in the instant claims is not limited to an invasin protein from any specific source, and therefore encompasses any invasin protein. As presented currently, instant claims do not exclude *Yersinia pseudotuberculosis*. Therefore, Applicants' argument is not commensurate in scope with what is recited in the claims. It is noted that the feature upon which Applicants rely is not recited in the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the limitation 'minimum concentration ...' is a relative term, and Paul *et al.* taught dialyzing the invasin protein solution using a buffer containing a reduced concentration of the protein denaturant, i.e., 6M urea as opposed to 9M urea. This meets the claim limitations in step f) of the instant claims. With regard to the rapid dilution, the preferable time within which the rapid dilution process is completed, as described at the top of page 29 of the specification, represents three examples, i.e., less than one minute, less than 30 seconds, and less than 10 seconds. Instant claims do not recite this time period. The non-limiting description for rapid dilution does not exclude the optimal dilutions described by Paul *et al.* to avoid aggregation during refolding. In fact, as noted by Applicants, the description at lines 19-20 and 20-24 on page 28 of the specification describes that '[w]ithout limiting the invention to any particular theory or mechanism, applicants believe that the rapid removal of denaturant allows beneficial protein intra-actions, necessary for correct protein folding, to occur while the rapid dilution of the protein solution minimizes the probability of detrimental protein-protein interaction, which form aggregates'. Therefore, 'rapid' removal as described in the instant specification is not required to take place within a time that is limited to less than one minute.

As set forth previously, Paul *et al.* taught a method for the production of a purified

recombinant soluble invasin protein which combines the use of a protein denaturant and affinity purification step. The prior art method comprises inserting a polynucleotide encoding an invasin protein into an expression vector; transforming a host cell with the vector; growing the transformed host cell under conditions suitable for soluble invasin expression; obtaining the invasin protein from the host cell lysate with a solution comprising guanidine hydrochloride (i.e., a protein denaturant); performing an affinity purification of the invasin protein using Hexahis-tag in the presence of 8M urea (i.e., a protein denaturant); dialyzing the invasin protein solution using a buffer containing 6M urea (i.e., a protein denaturant); and diluting the purified protein into a buffer solution that does not contain urea. As acknowledged by Applicants, Paul *et al.* taught that optimal dilutions were empirically determined to avoid aggregation during refolding. Clearly, the reducing of the concentration of urea from 8M to 6M represents retaining the protein denaturant concentration at the minimum concentration necessary to maintain the solubility of the purified invasion protein. The purified recombinant soluble invasin protein was shown, via an internalization assay, to retain its biological functions. See entire document, especially 'Materials and Methods' on pages 1254 and 1255, and 'Results' on pages 1256 and 1257. Paul's sequential dilution refers to sequential dilution of the dialysis buffer. Paul's diluted dialysis buffer was without urea or guanidine. Paul's dilution in this dialysis buffer clearly meets Applicants' non-limiting description in the instant specification of rapid removal of the denaturant, i.e., 'the rapid removal of denaturant that allows beneficial protein intra-actions, necessary for correct protein folding, to occur while the rapid dilution of the protein solution minimizes the detrimental protein-protein interaction, which form aggregates'. With regard to the step of 'dilution' in about 1 minute or less recited in claims 22 and 103, that such dilution in a denaturant-free solution occurs within about a minute in the prior art method, is inherent from the teachings of Paul *et al.* in light of the fact that the dilution process necessarily starts immediately with the beginning of the dialysis process in dialysis buffer free of urea or guanidine. It should be noted that 'about 1 minute' is not precisely defined in the instant specification and therefore the term 'about' encompasses 1 ± 10 minutes. The fact that Paul's final recombinant invasin protein product remained soluble (as opposed to aggregated) and biologically functional indicates that Paul's rapid dilution into a urea-free solution necessarily occurred within about 1 minute and avoided the detrimental protein-protein interaction and aggregate formation.

Contrary to Applicants' assertion, Paul *et al.* teach each and every element of claims 13 and 14, including removing the protein denaturant from the purified invasive protein until the concentration of the protein denaturant is at the minimum concentration necessary to maintain the solubility of the purified invasin protein (step f) and rapidly diluting the purified invasin protein into a volume of denaturant-free solution (step g). Clearly, Pauls' purification method anticipates the present invention. The rejection stands.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C § 112, Second Paragraph

33) Claims 13-18, 21, 22, 25 and 101-122 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 15 and 21 have improper antecedence in the recitation: '*the* affinity purification moiety' [Emphasis added]. Claims 15 and 21 depend from claim 14, which does not recite any 'affinity purification moiety'.

(b) Claims 13, 14 and 25 are indefinite, confusing and inconsistent in scope in the limitations: 'recombinant invasin protein' (see line 2), 'invasin protein' (see part a), and 'soluble invasin protein' (see part c), because it is unclear how one differs from the other in terms of scope. Does it mean that the 'recombinant invasin protein' recited in line 2 of the claim and the 'invasin protein' recited in part a) of the claim are not required to be soluble?

(c) Claims 13, 14 and 25 are indefinite in the limitation: 'an organism reconstituted from the transformed host cell' (see step d), because it is unclear what does this 'organism reconstitution' encompass. Does it mean that 'an organism reconstituted from the transformed host cell' results following step c) after growing of the transformed host cell under conditions conducive or conducive to soluble invasin protein expression? It is unclear how any 'organism', including a human or non-human animal organism, be 'reconstituted from the transformed host cell' in between step c and e of the claim.

(d) Claims 13, 14 and 25 are further indefinite and confusing in the limitation recited in step d): 'extracting the expressed invasin protein from a lysate of the transformed host cell'. Step d) follows step c) which includes growing the transformed host cell under conditions conducive or

conductive to soluble invasin protein expression. Does it mean that the step of growing the transformed host cell under conditions conducive or conducive to soluble invasin protein expression results in 'a lysate of the transformed host cell'?

(e) Claims 13, 14 and 25 are indefinite in the limitation 'the purified invasin protein' in steps f) and g) of the claims, because it is unclear where does the antecedence come from for the limitation. Lines 1 and 2 of the claims recite 'a purified recombinant invasin protein'. Step e) recites 'an affinity purification' of the extracted invasin protein. Is 'the purified invasin protein' recited in steps f) and g) of the claims the affinity-purified invasin protein, or does the antecedence for the above-identified limitation come from lines 1 and 2 of the claims? Clarification/correction is requested.

(f) Claims 106, 109, 113, 116 and 120 are vague and indefinite in the limitation: 'derived', because it is unclear what is encompassed in this recitation. Does the process of 'deriving' encompass: extraction, isolation, recombinant production, separation, dissociation, purification, modification, or expression on cell surface? The metes and bounds of what is encompassed in the limitation 'derived' are indeterminate. It is suggested that Applicants delete this limitation since it is unnecessary.

(g) Claims 15-18, 21, 22, and 101-122, which depend directly or indirectly from claim 13, 14 or 25, are also rejected as being indefinite due to the indefiniteness identified in the base claim.

Relevant Prior Art

34) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Prior *et al.* (EP 0 189 431) taught that the technique of genetic engineering whereby the DNA sequences coding for a protein are cloned and expressed in a host cell allows the production of large amounts of the protein, and identified the art-known fact that many genetically engineered proteins produced in the host cell are in the form of highly insoluble protein aggregates. Prior *et al.* taught a method of purifying proteins produced by genetic engineering techniques that form highly insoluble aggregates during growth of host cells transformed with DNA sequences coding for the proteins. Prior *et al.* taught transforming the host cells with DNA sequences coding

for a protein, expressing the sequence to cause the formation of the protein expression by growing the transformed cells under suitable conditions, extracting the expressed protein with a solution comprising a chaotropic agent such as urea or guanidine HCl (i.e., protein denaturant), performing chromatography, and including renaturing steps to remove the chaotropic agent by "rapid" dilution to reduce the chaotrope concentration such that the recombinant protein retains solubility and refolds to a stable native conformation followed by dilution with an aqueous PBS, i.e., a denaturant-free solution. Prior *et al.* expressly taught that chaotropic agents such as guanidine hydrochloride and urea are known in the art for their ability to solubilize insoluble protein aggregates and that they convert multiple protein aggregates into soluble individual proteins. Prior *et al.* taught the advantage of using the renaturation step by teaching that renaturing not only provides the recombinant protein in soluble native form, but separates the protein molecules from aggregate nucleic acid, phospholipids, and protein contaminants. See columns 5-7; Examples; and claims.

Remarks

35) Claims 13-18, 21, 22, 25 and 101-122 stand rejected.

36) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

37) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

38) Information regarding the status of an application may be obtained from the Patent

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Art Unit: 1645
October 2006


Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

39) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Acting Supervisor, Albert Navarro, can be reached on (571) 272-0961.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

October, 2006


S. DEVI, PH.D.
PRIMARY EXAMINER